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Prognostic value of coronary artery calcium scoring in patients with non-small cell lung cancer using initial staging computed tomography

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Abstract

Background Lung cancer is a leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) comprising 85% of cases. Due to the lack of early clinical signs, metastasis often occurs before diagnosis, impacting treatment and prognosis. Cardiovascular disease (CVD) is a common comorbidity in lung cancer patients, with shared risk factors exacerbating outcomes.

Methods This study investigates the association between coronary artery calcium (CAC) scores, major adverse cardiovascular events (MACE), and survival outcomes in NSCLC patients, utilizing positron emission tomography-computed tomography (PET-CT) for CAC scoring. A retrospective cohort study of 154 NSCLC patients (mean age 66.3 years, 52% women) at the University of Utah (2005–2022) was conducted. Baseline PET-CT or CT imaging was used to quantify CAC scores, categorized into five risk levels. Cox proportional hazards and logistic regression analyses assessed the impact of CAC scores on survival and cardiovascular events, adjusting for confounders such as age, gender, and smoking status.

Results Higher CAC scores were significantly associated with increased MACE, acute myocardial infarction (MI), and poorer overall survival. The severe risk CAC score group had significantly lower survival ($p = 0.022$). Logistic regression revealed a strong association between higher CAC scores and MI incidence (moderate: OR = 13.8, severe: OR = 21.2) and MACE (severe: OR = 10.2). Smoking history was a significant predictor of overall survival ($p = 0.006$).

Conclusion CAC scoring via PET-CT provides valuable prognostic insights in NSCLC patients, highlighting the need for integrated cardiovascular risk management in this population. Further research and advanced technologies like machine learning could enhance CAC scoring application in clinical practice.

Trial registration Retrospectively registered.

Keywords FDG-PET/CT, Coronary artery calcium scoring, Non-small cell lung cancer

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Introduction

Lung cancer stands as one of the leading malignant tumors globally, characterized by a high incidence and mortality rate. Non-small-cell lung cancer (NSCLC) emerges as the major pathological category, accounting for 85% of lung cancer cases [1]. Due to the lack of early distinctive clinical signs, metastasis to lymph nodes or distant sites frequently occurs prior to identification, having a significant impact on treatment options and prognosis [2]. For example, in the United States, the five-year survival rate for NSCLC patients is only 24%, dropping to 5.5% for those with distant metastases. Even among patients with resectable NSCLC, post-operative survival statistics are significantly lower, with only 60% surviving five years [3].

Despite advancements such as lung cancer screening via low-dose computed tomography (LDCT), discrepancies in outcomes persist between trials, underscoring the complexities of disease management [4]. Even if lung cancer is in its early stages, individuals may be at high risk for cardiovascular disease (CVD), as lung cancer and CVD share risk factors. CVD is the most common comorbidity in patients with lung cancer (23%), and its prevention should be a significant therapeutic priority [5]. Furthermore, the connection between cancer treatment and cardiovascular (CV) illness presents additional complexities, with little research focusing on patients with lung cancer [6]. Given the common risk factors and negative consequences of cancer therapy on cardiovascular health, a more thorough understanding could assist in optimizing the management strategies in this population.

Coronary artery calcium (CAC) scoring is now recognized as a vital tool in assessing cardiovascular risk, providing valuable prognostic insights beyond conventional risk factors, particularly regarding major adverse cardiovascular events (MACE) [7]. Despite this heightened risk, cardiac computed tomography (CT) is not routinely conducted in cancer patients. However, given its widespread use in cancer patients, positron emission tomography-computed tomography (PET-CT) offers a promising avenue for CACS calculation [8].

18 F-fluorodeoxyglucose positron emission tomography (18 F-FDG-PET), an imaging modality commonly used for cancer surveillance, quantifies 18 F-2-deoxy-d-glucose uptake within the artery wall (a correlate of atherosclerotic inflammation), which has emerged as a marker of atherosclerosis [9, 10]. Although studies have found a link between higher arterial FDG absorption and vascular events in people with active cancer, there is limited data evaluating its additional predictive value to established risk variables [11, 12]. Nonetheless, CACS derived from non-gated CT scans in PET myocardial perfusion studies have demonstrated good agreement with ECG-gated CT CACS, especially in higher CACS classes.

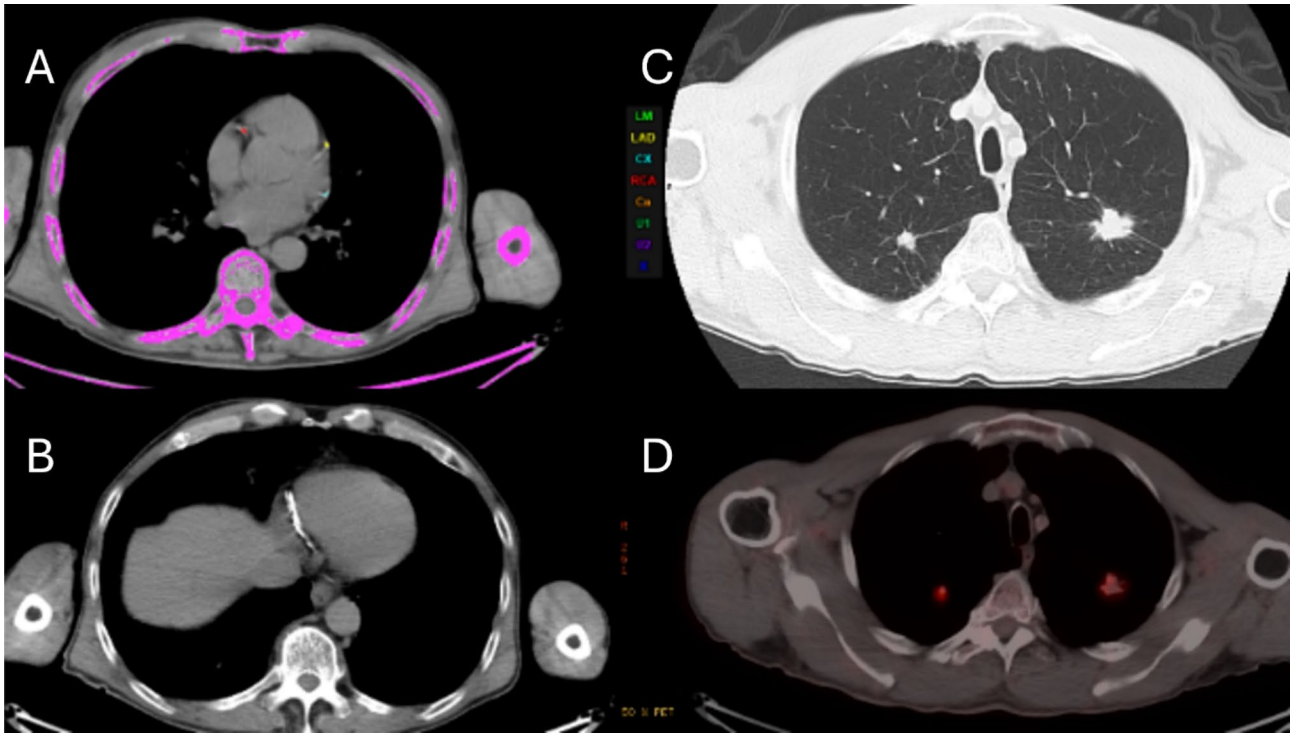

Fig. 1 A-D. User Interface of the Calcium Scoring Application. Images on the left (**A**, **B**) illustrate the application interface utilized for calcium scoring, showcasing a case from a 74-year-old with a total coronary artery calcium score of 3180. Images on the right (**C**, **D**) from the same patient depict a spiculated non-small cell lung cancer in the left upper lobe and a smaller metastasis in the right upper lobe, both FDG-avid

Table 1 Demographic and clinical characteristics by calcium score risk

Calcium Score Risk	Number of cases	Average of Age ± std. dev (yrs)	Female: Male	+ Family Hx of Lung Cancer[2]	+ Hx of COPD	+ Hx of Smoking	+ Hx of CABG or PCI	+ Hx of MACE	+ Hx of Acute MI	Median F/U Days (IQ[3] 25 – IQ 75)
No Risk	71	61.5 ± 11.7	50:21	8	12	25	0	6	2	1254 (429–1993)
Minimal Risk	13	65.8 ± 5.9	7:6	2	3	7	0	2	0	902 (275–2349)
Mild Risk	25	67.5 ± 7.5	11:14	7	6	18	0	7	2	888 (360–1891)
Moderate Risk	12	72.7 ± 8.8	3:9	0	3	8	0	3	2	722 (336–722)
Severe Risk	33	73.8 ± 7.1	10:23	2	18	30	11	14	7	506 (242–1587)

According to the 2016 SCCT/STR guideline. Family Hx wasn't available for 1 patient. IQ: interquartile

While FDG-PET is frequently used in cancer staging, this study specifically focuses on CT-derived coronary artery calcium (CAC) scoring, which was obtained as part of routine PET-CT imaging.

Methods

The study protocol was approved by the Institutional Review Board of the University of Utah (IRB_00157206). The need for patient consent was waived by the IRB. Deidentified data are available from the corresponding author only upon reasonable request.

Study Population

This retrospective cohort study included 154 patients < 90 years of age diagnosed with NSCLC who underwent baseline staging with PET-CT ($n=129$) or CT alone ($n=25$) at the University of Utah between 7/25/2005 and 9/3/2022. Eligible participants were adults aged 18 years or older with a confirmed diagnosis of NSCLC on biopsy. A small number of patients had one or more coronary artery stents ($n=15$) and/or coronary artery bypass grafting ($n=7$) prior to NSCLC diagnosis. A small number of patients received intravenous contrast with their initial staging PET/CT or chest CT ($n=19$).

Data Collection

Clinical, demographic, and follow-up survival data were extracted from electronic health records. Variables collected included age, race, sex, body mass index (BMI), smoking history, pre-existing cardiovascular disease (coronary artery disease, dyslipidemia, prior CABG, prior percutaneous coronary intervention, carotid artery disease, aortic aneurysm, sustained atrial or ventricular arrhythmias, valvular heart disease, heart failure, cardiomyopathy, pericardial disease, stroke, transient ischemic attack, and peripheral artery disease), cancer histology, stage, size, and follow-up outcomes. Cardiac events included acute MI, unstable angina, CABG, PCI, stroke, PE/DVT, heart failure, arrhythmias, cardiovascular death, major adverse cardiac events (MACE), and all-cause mortality were recorded. MACE was defined as acute MI, stroke, cardiovascular death, unstable angina, or heart failure, according to the U.S. Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (2017) [13].

Imaging analysis

Staging imaging of the chest was performed using either a SOMATOM FORCE CT scanner or a Biograph 64_vision 600 PET/CT scanner (Siemens Healthineers, Malvern, PA, USA). SOMATOM FORCE CT scanner protocol was a follows: for most patients the exam was performed without administration of intravenous (IV) contrast; for those receiving IV contrast, scanning was started 25 s after injection of 100mL of intravenous iodinated contrast (Omnipaque 350, GE Healthcare, Marlborough, MA); scanning during inspiration from above the lung apices to below the adrenal glands, rotation time 0.28 s, thickness 3.0 mm, pitch 2.0, interval 3.0 mm, CARE kV, CARE Dose 4D, with standard soft tissue reconstruction kernel (Br40) at 3.0 mm slice thickness.

Patients undergoing [18 F]Fluciclovine PET/CT imaging received a 10 mCi (+20%) dose while positioned supine on the scanner with arms overhead. Scanning, from upper thigh to skull base (20–30 min), was conducted with PET detector resolution of 3.7 mm (transaxially/axially) 4×5×5 arrays of 3.2×3.2 mm LSO crystals with 16 SiPMs and CT spiral acquisition parameters of 0.6 mm collimation width, 19.2 mm total collimation width, 86 s exposure with pitch factor of 0.55, using one X-ray source and a 3-mm slice reconstruction.

CT imaging was reviewed retrospectively for each patient by two radiologists (JRB, NQ). The CAC scores were automatically quantified using Syngo.*Via* (Siemens Healthineers, Malvern, PA, USA). Each study was uploaded to Syngo.*Via* and the CAC score was quantified using the CT Ca scoring application in the CT Cardiac package. The predictive value of FDG uptake (SUV) was not evaluated in this analysis. CAC results were confirmed by a level III COCAT trained radiologist with 23 years of experience in cardiac imaging (JRB) and CAC scores were classified according to the 2016 SCCT/STR guidelines into the following categories: no risk (0), minimal (1–10), mild (11–100), moderate (101–400), and severe (>400). These categories were used to assess cardiovascular risk in the patient population [14] (Fig. 1).

Imaging for CAC scoring was done at the initial NSCLC staging time point. The 17 patients with a history of previous stent insertion or CABG were included in the severe risk class. Patients who received intravenous contrast with their staging PET-CT or chest CT had CAC scores calculated according to the Otton method [15].

Statistical analysis

Patients were stratified based on their CAC scores for analysis. Cox proportional hazards regression and Kaplan-Meier models were employed to assess the impact of CAC scores on survival outcomes. Univariate and multivariate Cox proportional hazards analyses were conducted to assess the impact of calcium score categories, smoking history, age, and sex on survival outcomes, MACE and MI in patients with NSCLC. The models were then adjusted for potential confounders such as age, gender, and smoking status. Logistic regression with adjustments for potential confounding (i.e., age, sex, smoking history) was used to examine the relationship between CAC scores and the incidence of MACE and acute myocardial infarction (MI). Logistic regression models were adjusted for key confounders, including age, gender, and smoking history, to assess the independent effects of CAC scores on MACE and MI. Baseline ejection fraction (EF) was extracted from available clinical records at the time of NSCLC diagnosis to explore its impact on survival. The significance level was set at $p<0.05$. The area under curve (AUC) of the receiver operating characteristic (ROC) curve was then calculated for each regression model. All the statistics were performed using IBM SPSS version 29.

Results

Of the 154 NSCLC patients, the mean age was 66.3±10.8 years, 81 (52%) were women, and 66 (42.9%) were never smokers. 76 patients (49.3%) died during a mean follow-up time of 6.2±2.7 years. The details of the demographic data are found in Table 1. Table 2 depicts the distribution of AJCC 8th Ed stage among different calcium score groups. Figure 2 depicts the occurrence of each major cardiovascular event in our population.

The median time of follow-up across the cohort was 911 days (Range: 10–7196 days). Cox regression analysis revealed a statistically significant poorer survival for patients in the severe CAC score group (*P*-value=0.022) (Table 3). Figure 3 shows the Kaplan-Meier Curve of the survival analysis based on calcium score.

Logistic regression analysis showed a significant association between the calcium score and the incidence of acute myocardial infarction (MI) in CAC score classes moderate (*P*-value=0.039) and severe (*P*-value=0.005) (Table 4). The odds ratio (OR) of this association is estimated to be 13.8 (95% CI: 1.14–166.5) for the moderate

Table 2 Distribution of AJCC 8th Ed stage among different calcium score classes

AJCC 8th Ed stage												
Calcium Score	**IA1**	**IA2**	**IA3**	**IB**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IIIC**	**IVA**	**IVB**	**Grand Total**
No Risk	1	9	1	5	1	6	6	2	2	19	19	71
Minimal Risk		2		1		2	1	1		2	4	13
Mild Risk		2	1	3	2	1	1	2		5	8	25
Moderate Risk		4			3	1		1	1	2		12
Severe Risk	2	2	1	4	1	1	7	4	2	5	4	33
Grand Total	**3**	**19**	**3**	**13**	**7**	**11**	**15**	**10**	**5**	**33**	**35**	**154**

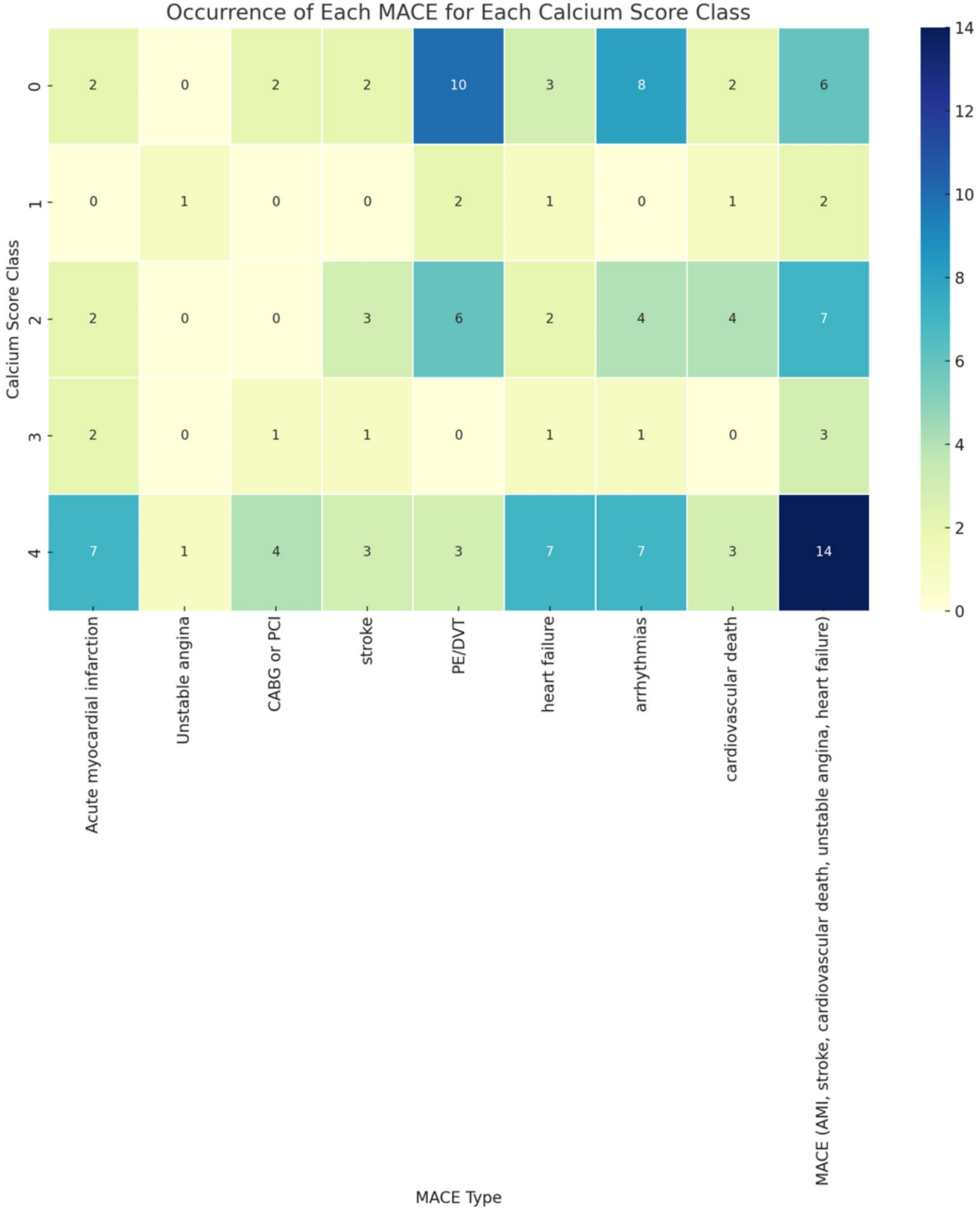

Fig. 2 Heatmap illustrating the number of patients with each major adverse cardiovascular event. Each patient could have multiple events

Table 3 Cox regression analysis for the comparison between survival rates of different calcium score

	P-value	OR	95.0% CI for OR*	
			Lower	Upper
No Risk	0.109			
Minimal Risk	0.915	0.950	0.370	2.441
Mild Risk	0.160	1.540	0.843	2.813
Moderate Risk	0.447	0.573	0.137	2.403
Severe Risk	0.022	1.911	1.099	3.324

* Odds Ratio

Table 4 Logistic regression analysis for Predicting AMI by Calcium score

			95.0% CI for OR*	
	P-value	OR	Lower	Upper
No Risk	0.061			
Minimal Risk	0.999	0.000	0.000	
Mild Risk	0.151	6.00	0.52	69.2
Moderate Risk	**0.039**	**13.80**	1.14	166.5
Severe Risk	**0.005**	**21.23**	2.5	178.1
Constant	< 0.001	0.014	0.014	

OR: Odds Ratio

Table 5 Logistic regression analysis for Predicting MACE by Calcium score

	P-value	OR*	95% C.I.for OR	
			Lower	Upper
No Risk	0.002			
Minimal Risk	0.338	2.364	0.407	13.737
Mild Risk	0.012	5.056	1.433	17.837
Moderate Risk	0.071	4.333	0.882	21.294
Severe Risk	< 0.001	10.263	3.303	31.895
Constant	< 0.001	0.077		

* OR: Odds Ratio

class and 21.2 (95% CI: 2.5–178.1) for the severe group. The receiver operator characteristic (ROC) curve of the mentioned association revealed an area under the curve (AUC) of 0.79 (*P*-value=<0.001) for the prediction of acute MI (Fig. 5). There also was a significant association between CAC score and major adverse cardiovascular events (MACE) in the severe class (*P*-value=<0.001), though not significant in the moderate group (*P*-value=0.071). The OR of this association was estimated to be 4.3 (95% CI: 0.9–21.3) for the moderate class and 10.2 (95% CI: 3.3–31.9) for the severe class (Table 5). The ROC curve of the mentioned association revealed an AUC of 0.74 (*P*-value=<0.001) for the prediction of MACE in this cohort (Fig. 5). History of smoking (whether current or former smoker) was a significant predictor of the overall survival in this population (*P*-value=0.006) (Fig. 2). Patients without a smoking history had a mean survival of 9.1 years (95% CI: 6.6–11.5), compared to 4.4 years (95% CI: 3.5–5.3) for smokers. Similarly, the median survival was 6.9 years (95% CI: 5.5–8.3) for non-smokers and 4.0 years (95% CI: 2.7–5.4) for smokers. Figure 4 depicts the Kaplan-Meier curve of

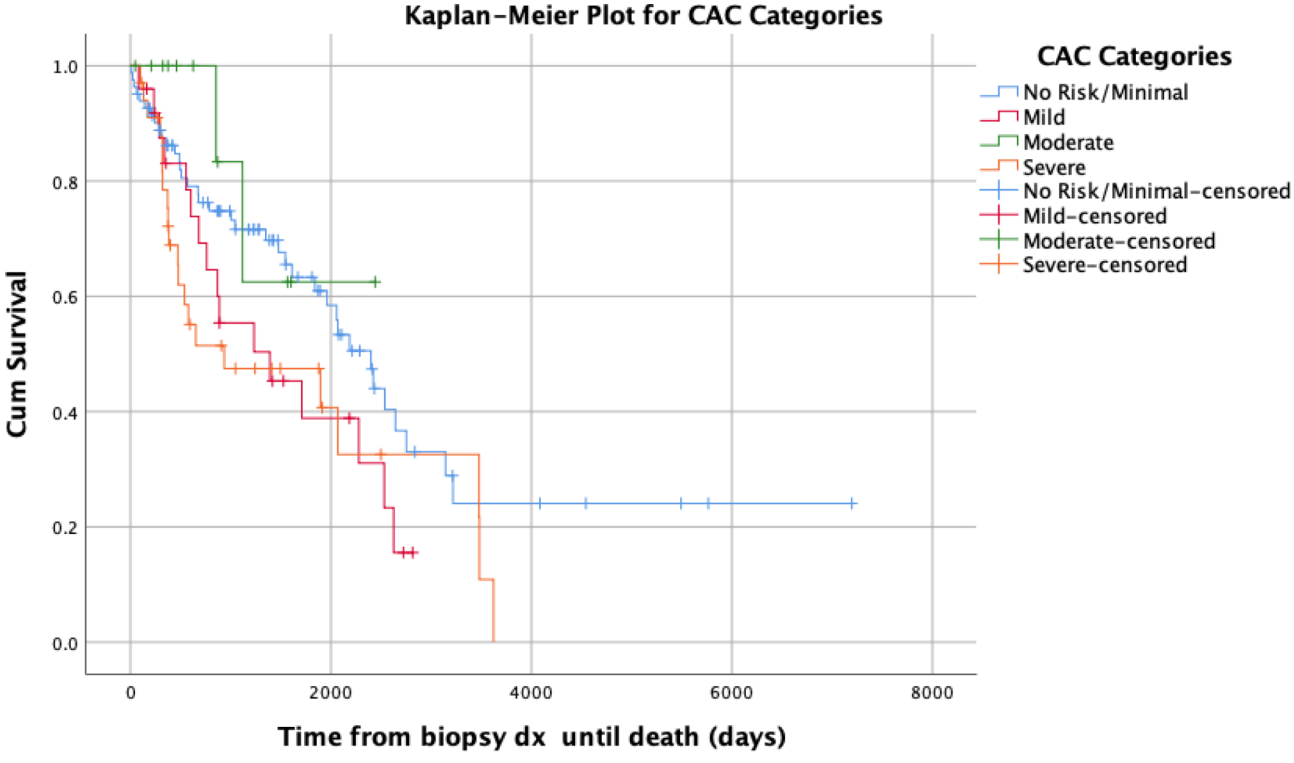

Fig. 3 Kaplan-Meier plot for illustrating overall survival for different calcium Scoring classes

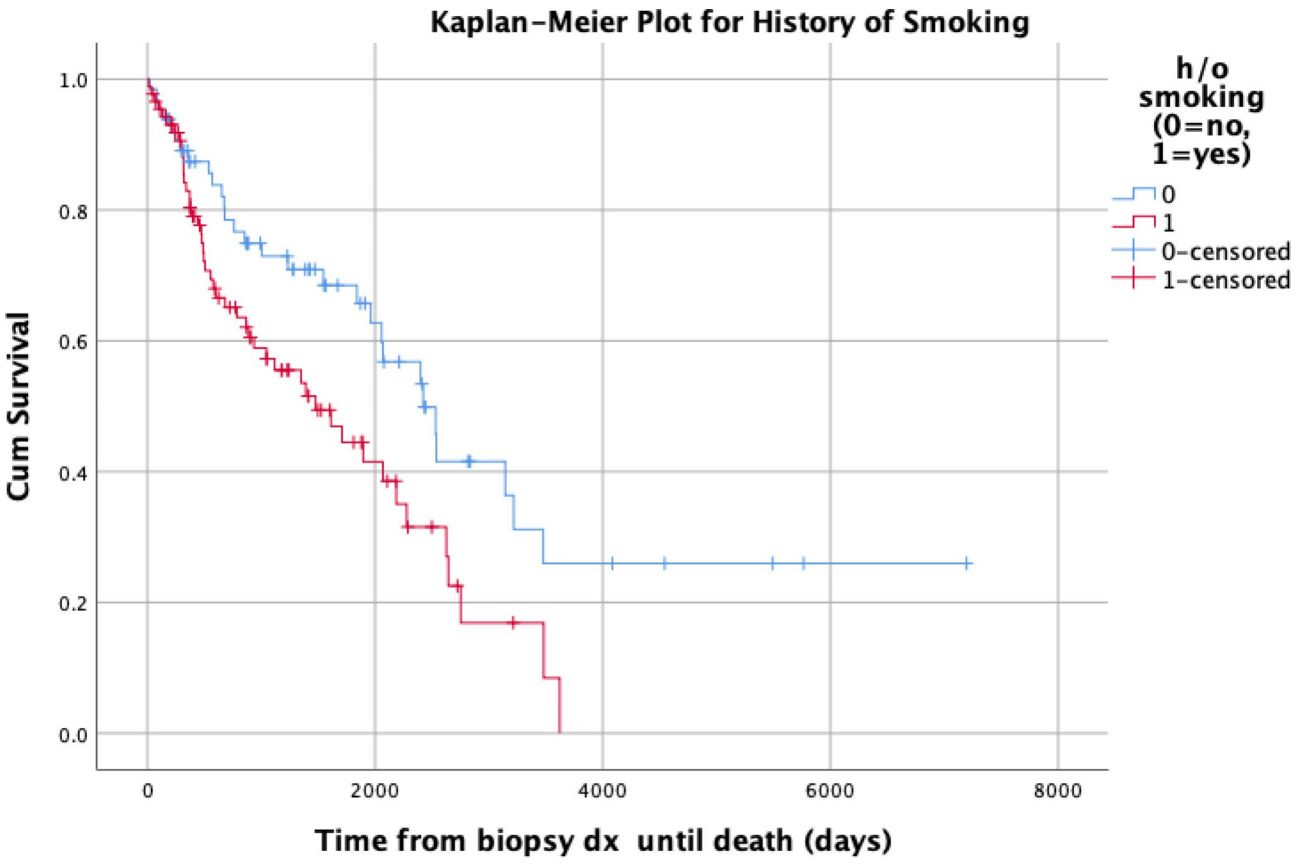

Fig. 4 Kaplan-Meier plot for illustrating the comparison between the overall survival of patients with a history of smoking vs. never-smokers

Fig. 5 Receiver operating characteristic curve (ROC) for (**a**). Predicting acute myocardial infarction (AMI) using CAC Scores on staging PET/CT and (**b**). Predicting major adverse cardiovascular events (MACE) using CAC scores on staging PET/CT

the survival analysis for the history of smoking. Baseline ejection fraction (EF) at the time of lung cancer diagnosis was not a significant predictor of survival (*P*-value: 0.32).

Discussion

The results of our study indicate a significant correlation between CAC scores quantified using standard staging PET-CT or chest CT and acute myocardial infarction, major adverse cardiovascular events (MACE), as well as all-cause mortality in patients with non-small-cell lung cancer (NSCLC). Even after controlling for potential confounding variables such as age, gender, and smoking status, the association between CAC scores and MACE remained statistically significant. These findings are consistent with prior research that highlights the importance of CAC scoring in assessing cardiovascular risk beyond traditional risk factors [16–18].

Many studies have emphasized the usefulness of CAC scoring as a crucial tool for cardiovascular risk stratification in the general population [19–21]. For instance, a study by McClelland et al. (2015) published in the Journal of the American College of Cardiology found that CAC scoring is a significant predictor of cardiovascular events and provides incremental information over traditional risk factors [22]. This supports our findings and suggests that CAC scoring could potentially be more broadly applied in clinical settings where cardiovascular disease may intersect with other chronic conditions, such as lung cancer [23, 24]. The concept of the utilization of low-dose CT for cardiovascular risk assessment has been offered by previous studies [24, 25]. Finding a significant correlation between CAC scores and the incidence of acute myocardial infarction (MI) in patients with NSCLC emphasizes the importance of cardiovascular risk assessment in this population, especially for those with higher CAC scores.

Moreover, our study showed that a history of smoking was a significant predictor of overall survival in NSCLC patients, which is consistent with prior research indicating smoking as a substantial risk factor for lung cancer and cardiovascular disease [26, 27]. These findings emphasize the detrimental effect of smoking, reinforcing the need for integrated cardiovascular and oncologic care in smokers with NSCLC.

The utilization of positron emission tomography-computed tomography (PET-CT) for CAC scoring in our study highlights its feasibility and potential to improve patient outcomes by integrating cardiovascular assessment into the routine evaluation of cancer patients. This could help identify NSCLC patients who require more intensive cardiovascular monitoring and management and potentially improve outcomes. Prospective evaluation of this hypothesis is needed.

Our study has limitations that need to be acknowledged. Firstly, the retrospective design and the sample size of 154 NSCLC patients, although adequate for initial observations, may not provide sufficient power to detect smaller effect sizes or to conduct extensive subgroup analyses, which can limit the generalizability of our findings. Another concern is the variability in the methods used for CAC scoring, especially considering that some patients received scans with intravenous contrast, which could affect the accuracy and reproducibility of CAC quantification. However, we knowingly included these patients to include as many real-world variables in our study as possible to extend the applicability of our findings. There may be unmeasured confounders that we could not account for, which might influence the observed relationships between CAC scores, cardiovascular events, and survival outcomes. Although we collected data on cancer stages and histopathological types the sample size within these subgroups was insufficient for robust statistical analysis. Incorporating these variables as potential confounders in our survival models would have provided deeper insights into the relationship between cardiovascular risk, cancer characteristics, and survival outcomes. However, the small numbers in these categories limited our ability to perform reliable stratified or multivariate analyses. Furthermore, the single-center nature of the study might limit the applicability of the results to other settings due to potential differences in patient demographics, treatment approaches, and healthcare systems.

Our findings underscore the need for further research into the integration of CAC scoring in the management of NSCLC to enhance patient care and outcomes, particularly in integrating comprehensive cardiovascular risk management with cancer treatment strategies. New technologies utilizing advanced computing technologies such as machine learning and deep learning algorithms would likely enhance the integration of CAC scoring in the management of NSCLC, as well as other forms of cancer, by automating the process.

Conclusion

This study highlights the prognostic value of CT-derived coronary artery calcium (CAC) scoring in non-small cell lung cancer (NSCLC) patients. Higher CAC scores were associated with increased risk of major adverse cardiovascular events (MACE), myocardial infarction (MI), and reduced overall survival, independent of traditional risk factors such as age, gender, and smoking. Integrating cardiovascular risk assessment into cancer management may improve patient outcomes. Future studies could further explore the potential of FDG-PET and automated imaging technologies in enhancing risk prediction and care delivery.

Abbreviations

- NSCLC Non-small cell lung cancer
- CVD Cardiovascular disease
- CAC Coronary artery calcium
- MACE Major adverse cardiovascular events
- PET CT-positron emission tomography-computed tomography
- MI Myocardial infarction
- CT Computed tomography
- BMI Body mass index
- CABG Coronary artery bypass grafting
- PCI Percutaneous coronary intervention
- PE/DVT Pulmonary embolism/deep vein thrombosis
- CTCAE Common terminology criteria for adverse events
- ROC Receiver operating characteristic
- AUC Area under curve
- EF Ejection fraction
- FDG PET-fluorodeoxyglucose positron emission tomography
- IRB Institutional review board
- AJCC American joint committee on cancer

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None.

Author contributions
AZ-substantial contributions to analysis and interpretation of data; drafted the work and revised it. MG- substantial contributions to drafting the work and revised it. GS- substantial contributions to statistical analysis, revision. PSA-substantial contributions to analysis. LW-substantial contributions to analysis. AN-substantial contributions to analysis. MRC-substantial contributions to analysis. LW- substantial contributions to analysis, revision. MI-substantial contributions to revision. JC- substantial contributions to revision. WFA- substantial contributions to revision. IK-substantial contributions to analysis, drafting the work and revision. JRB- substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data; assisted with drafting the work. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Institutional Review Board of the University of Utah (IRB_00157206). Due to the retrospective nature of the study, patient informed consent was waived. Deidentified data are available from the corresponding author only upon reasonable request. The need for patient consent to participate was waived by the IRB.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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